CDC FACT SHEET

# CDC TRIALS OF DAILY ORAL TENOFOVIR FOR PREVENTING HIV INFECTION

## Phase II and III Clinical Trials in Botswana, Thailand and the United States

New approaches to HIV prevention are urgently needed to stem the estimated five million new HIV infections that occur worldwide each year. While behavior change programs have contributed to dramatic reductions in the number of annual infections in the U.S. and many other nations, far too many individuals remain at high risk. With an effective vaccine years away, there is mounting evidence that antiretroviral drugs may be able to play an important role in reducing HIV infection. As part of its commitment to developing new HIV prevention strategies, the Centers for Disease Control and Prevention (CDC) is sponsoring three clinical trials of the antiretroviral drug tenofovir disoproxil fumarate (or "tenofovir," brand name "Viread®").

The trials are designed to answer important questions about the safety and efficacy of tenofovir as a daily oral HIV preventative among three populations at high risk for infection: heterosexuals in Botswana, intravenous drug users in Thailand and men who have sex with men in the United States. The trials in Botswana and Thailand are Phase II/III safety and efficacy trials, while the U.S. trial is a smaller, Phase II extended safety trial. All three sites will also assess the effects of taking a daily pill on HIV risk behaviors, adherence to and acceptability of the regimen, and in cases where participants become HIV infected, the resistance characteristics of the acquired virus. This information will be critical to guide future studies and HIV prevention programs.

Similar HIV prevention trials of tenofovir are also being planned or are underway among high-risk populations in Ghana, Nigeria, Cameroon, and Malawi. These trials are being conducted by researchers at Family Health International with funding from the Bill and Melinda Gates Foundation.


WHERE CDC TENOFOVIR TRIALS ARE TAKING PLACE

# Rationale for Tenofovir HIV Prevention Trials

Researchers believe that tenofovir, taken as a daily oral preventative, is one of the most important new prevention approaches being investigated today. An effective daily preventative could help address the urgent need for female-controlled prevention methods and, when combined with existing prevention measures, could help reduce new HIV infections among men and women at high risk.

The concept of providing a preventative treatment before exposure to an infectious agent is not new. For example, when individuals travel to an area where malaria is common, they are advised to take medication to fight malaria before and during travel to that region. The medicine to prevent illness is then already in their bloodstream if they are exposed to the infectious agent that causes malaria.

Several sources of data suggest that the use of antiretroviral drugs in this manner may be effective in reducing the risk of HIV infection. Theoretically, if HIV replication can be inhibited from the very first moment the virus enters the body, it may not be able to establish a permanent infection. Providing antiretrovirals (ARVs) to HIV-infected women during labor and delivery and to their newborns immediately following birth has been shown to reduce the risk of mother-to-child transmission by about 50%. Additionally, in observational studies, ARV regimens have been associated with an 80% reduction in the risk of HIV infection among health care workers following needle sticks and other accidental exposures, when treatment is initiated promptly and continued for several weeks. Finally, animal studies have shown that tenofovir can prevent the transmission of a virus similar to HIV in monkeys when given before and immediately after a single retroviral exposure. These data, combined with its favorable resistance and safety profile as an HIV treatment, make tenofovir an ideal candidate for HIV prevention trials.

### Tenofovir Characteristics

- Established safety as HIV treatment
- Potent antiretroviral
- Long duration of action
- Once-daily dosing
- Low level of resistance

Tenofovir was approved by the U.S. Food and Drug Administration in 2001 as a treatment for HIV infection and has been used by more than 150,000 people with HIV around the world. As a treatment for HIV-infected individuals, tenofovir has been shown to be both safe and effective. It has a relatively low level of side effects and a slow development of associated drug resistance, compared with other available HIV treatments. The most common side effects include nausea, vomiting and loss of appetite. Because it is taken orally only once a day, with or without food, it is also one of the most convenient-to-use HIV drugs available today. These trials are designed to evaluate tenofovir's safety and efficacy among uninfected individuals. Side effects may differ in HIV-negative populations, and it is not yet known if tenofovir can prevent HIV infection in humans.

# Specific Trial Designs and Objectives

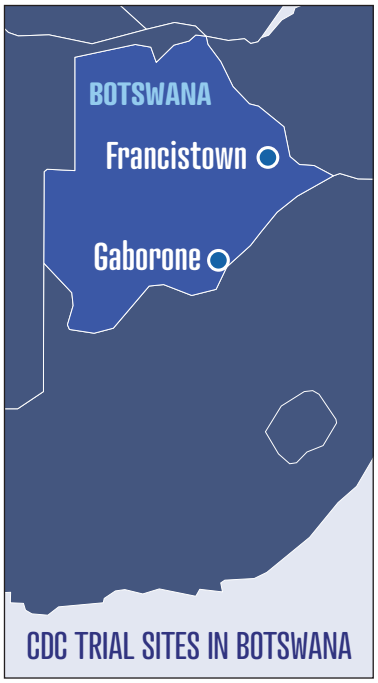
All three of CDC's studies are randomized, double-blind, placebo-controlled trials. In each trial, all participants will receive risk-reduction counseling and other prevention services. In addition, half of the participants will be randomly assigned to take one 300 mg tenofovir pill daily, and the other half will be randomly assigned to take one daily placebo pill (a similar tablet without active medication). Neither researchers nor participants will know

an individual's group assignment. In all, the studies will involve 3,200 volunteers. The studies are scheduled to begin in early 2005, and are expected to last between 2 and 4 years.

To ensure that the studies remain on a solid scientific and ethical foundation, all study procedures and plans are reviewed and approved by scientific and ethical review committees at CDC (called institutional review boards, or IRBs), as well as IRBs established by each host country and research site prior to trial launch. Additionally, data on safety, enrollment, and efficacy will be reviewed at standard intervals by an independent data safety and monitoring board (DSMB) for the Botswana and Thai trials, and by an independent safety review committee for the U.S. trial, to ensure that the research is safe to continue. During the Phase III components, the DSMB will also determine at what point the results are conclusive. If scientific questions arise during the course of the research, these committees will meet more frequently.

# Botswana and Thailand

The trials in Botswana and Thailand are Phase II/III safety and efficacy trials. This means that each trial will begin by examining safety alone (Phase II) among local HIV-uninfected participants. After participants have completed a pre-determined amount of follow-up (200 patient-years of observation), data will be assessed bythe DSMB. If the DSMB determines that the once-daily regimen is safe for participants, the trials will be expanded to assess efficacy (Phase III) in addition to continued safety monitoring.


■ **Botswana** — The Botswana study is being conducted in collaboration with the Botswana government and will enroll 1,200 HIV-negative heterosexual men and women, ages 18 to 29, in the nation's two largest cities, Gabarone and Francistown. Participants will be recruited through a number of venues, including HIV voluntary counseling and testing centers, sexually transmitted disease (STD) and family planning clinics, youth organizations, and community events.

■ **Thailand** — The Thailand study is being conducted in collaboration with the Bangkok Metropolitan Administration and the Thailand Ministry of Public Health and will enroll 1,600 HIV-negative intravenous drug users (IDUs) at 17 drug-treatment clinics in Bangkok. Participants will be recruited at the drug treatment clinics and through a peer referral program.

# The United States

The U.S. trial is a Phase II trial designed to assess the clinical and behavioral safety of once-daily tenofovir among HIV-negative men who have sex with men (MSM). Efficacy will not be examined in this study as a much larger sample would be required to determine efficacy in this population. Following completion of the safety component, data from this study will assist in the design of future studies among MSM, and will provide critical information to guide the development of guidelines for use, should efficacy be demonstrated in other populations.


■ **United States** — The U.S. study is being conducted at two sites in collaboration with the San Francisco Department of Public Health and the AIDS Research Consortium of Atlanta. The study will enroll 400 HIV-negative MSM who report having had anal intercourse in the past 12 months. Participants will be randomly assigned to one of four study arms. Two arms will receive either tenofovir or placebo immediately, while the other two arms will receive either tenofovir or placebo after nine months of enrollment. This design will allow researchers to compare risk behaviors among those taking a daily pill and those not taking pills.

# Education and Enrollment of Trial Participants

Understanding the potential impact of a daily drug regimen on HIV risk behaviors will be critical, should tenofovir prove effective in reducing HIV transmission. One of the greatest risks, as efforts progress to identify new biomedical approaches, is that individuals at risk will reduce their use of proven HIV prevention strategies. It will therefore be crucial to reinforce proven behavioral prevention strategies, both within and beyond these trials. All three trials will take multiple steps to address this issue during the education and enrollment of trial participants and through ongoing participant counseling.

First, it is critical to ensure that participants understand that trial participation may not protect them from HIV infection—either because they may receive a placebo or because they may receive tenofovir, the efficacy of which remains unproven. This and other key aspects of the trial, including the potential risks and benefits of participation, are explained to potential volunteers in depth in the language of their choice, prior to their enrollment. To ensure participants fully understand all aspects of their participation, all volunteers will be required to pass a comprehension test prior to providing written informed consent. Study participants are also free to withdraw from the trial at any time and for any reason.

# Risk-Reduction Counseling and Other Prevention and Treatment Services

To assist participants in eliminating or reducing HIV risk behaviors, extensive counseling will be provided at each study visit, and more often if needed. The interactive counseling to be provided has proven effective in reducing the risk of HIV and other STDs in multiple populations, including past participants of similar HIV prevention trials. Participants will also be offered free condoms and STD testing and treatment to reduce their risk for HIV infection. Additionally, in Thailand, participanting IDUs will be offered follow-up in a methadone drug treatment program and receive bleach and instructions on how to use it to clean needles. Consistent with Thai government policy, sterile syringes will not be provided, but are widely available in Thailand without a prescription and at low cost (one sterile syringe and one needle cost about 5 baht, or about $0.12).

While participants will likely be at lower risk as a result of these prevention services, some individuals will engage in behavior that places them at risk for HIV infection. To ensure that participants who are infected during the trial are quickly referred to the best available medical and psychosocial services, participants will receive free rapid HIV testing at every visit. This regular HIV testing will also help guard against the development of drug-resistant virus, as tenofovir will be immediately discontinued when infection is detected.

Participants who become infected will receive confirmatory testing for infection, post-test risk-reduction and support counseling, and help enrolling in local HIV care programs. Both Thailand and Botswana have antiretroviral treatment and HIV care programs in place at minimal or no cost to patients. In the United States, participants will be referred to local health care providers or public programs for needed medical and social services.

To help guide treatment decisions and to determine if prior exposure to tenofovir has any effect on the course of disease, participants will be followed for an additional 12 months following infection, and testing will be provided for viral load, CD4 count, and HIV resistance mutations. Because resistance to tenofovir is relatively uncommon among HIV-infected individuals using the drug for treatment, researchers believe that the probability of participants either becoming infected with, or developing, drug-resistant virus during the trial will be low. However, resistance testing will provide important data on the degree to which any resistance occurs.

# Monitoring for Side Effects

The health of participants will be closely monitored throughout the trial, and participants will be linked to any necessary medical care as needed. In addition to scheduled reviews of safety data by the DSMB, both clinical and behavioral safety will be closely monitored on an ongoing basis. Although tenofovir has an excellent safety profile, potential medical risks include minor side effects such as nausea, rash and gastrointestinal effects, as well as the potential for rare but more serious effects, such as damage to kidney function or reductions in bone density. Careful monitoring will be provided using laboratory testing for any biological abnormalities (such as elevated creatinine or decreased phosphorus), so that tenofovir can be promptly discontinued if serious concerns are identified. CDC will work with partners in each community to ensure that care is provided if tenofovir results in any health problems during the trial.

# Community Involvement

CDC has and will continue to work closely with community partners at each research site to ensure active community participation during the planning and implementation of these trials.

■ **Botswana** — In Botswana, community advisory boards have been established at each site, which include representatives from local governments (elected and traditional), as well as community members and representatives from key stakeholder organizations. These groups will provide input to researchers throughout the trial. Participant advisory boards will also be set up when the trial begins.

■ **Thailand** — In Thailand, a community relations club, made up of intravenous drug users, their family members, and representatives of local community organizations, meets regularly and provides advice to study staff on all aspects of study design and implementation.

■ **United States** — In the United States, both sites have established active community advisory boards that are consulted regularly about study procedures and educational materials for potential participants. Members of these boards will provide ongoing advice throughout the trials.

In addition to the regular input received by these established committees, broader outreach and consultations with advocates and community-based organizations representing populations at risk for HIV are being held, as needed, to address current and future plans for HIV prevention research and programs.

# Next Steps in HIV Prevention

As we move forward with our search for new HIV prevention strategies, it will be critical to determine how these approaches can best be integrated into existing programs, should they prove effective in reducing risk. Because no strategy will be 100% effective in preventing HIV infection, future impact will ultimately be determined by how effectively strategies are used in combination to provide the greatest protection to individuals at risk. CDC, in collaboration with the World Health Organization, the National Institutes of Health, other research organizations, and community stakeholders worldwide, is developing plans to quickly respond to emerging data from these and other HIV prevention trials. These collaborations will help guide the development of future policies and programs that can most effectively reduce the toll of HIV and AIDS.